

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

## PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2004/043451

International filing date (day/month/year)  
22.12.2004

Priority date (day/month/year)  
23.12.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D417/12, C07D417/14, C07D498/04, C07D263/56, C07D271/06, C07D413/12, A61K31/54, A61P17/06

Applicant  
AXYS PHARMACEUTICALS, INC.

**1. This opinion contains indications relating to the following items:**

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Weisbrod, T

Telephone No. +49 89 2399-8931



**WRITTEN OPINION OF THE  
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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material:  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing:  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 5-17

because:

- ☒ the said international application, or the said claims Nos. 5-17, relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-18
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-18
Industrial applicability (IA)	Yes: Claims	1-4,18
	No: Claims	

2. Citations and explanations

see separate sheet

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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**Box No. VII Certain defects in the international application**

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The following defects in the form or contents of the international application have been noted:

see separate sheet

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/043451

**Re Item I**

**Basis of the opinion**

The application is directed to

- (i) amidino compounds of formula (I) (claims 1-3),
- (ii) a pharmaceutical composition comprising compound (I) (claim 4),
- (iii) therapeutic methods involving compounds (I) (claims 5-17), and
- (iv) the medical use of compounds (I) (claim 18).

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 5-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

- 1 Reference is made to the following documents.

D1: WO 2004/000838 A, 31 December 2003.

D2: WO 2004/108661 A, 16 December 2004.

D3: WO 02/098850 A, 12 December 2002.

D4: WO 02/20485 A, 14 March 2002.

D5: WO 03/029200 A, 10 April 2003.

Documents **D1** and **D2** were published after the priority date. Under the presumption that the priority is valid for the claimed matter these documents are not considered as prior art under Rule 64.1 PCT.

- 2 Novelty

2.1 **D3** relates to inhibitors of cysteine proteases in particular of cathepsin S. The compounds of **D1** generally comprise already certain present compounds (I) (cf. **D1**, claim 1:  $X^1 = -NHCR^1R^2X^3$ ;  $R^1 = C_{1-6}$ alkyl;  $R^2 = H$ ;  $X^3 = CR^7R^8R^{16}$ ;  $R^7+R^8 = O$ ;  $R^{16} = C_{5-10}$ heteroaryl;  $R^3 = X^5SO_2R^{14}$ ;  $X^5 = \text{a bond}$ ;  $R^{14} = C_{5-10}$ aryl- $C_{0-6}$ alkyl;  $X^7 = H$ ;  $X^2 = NHR^{15}$ ;  $R^{15} = C_{5-10}$ heteroaryl). The document, however, does not specifically exemplify compounds wherein  $R^{15}$  is identical with the fragment  $-C(=NR^5)R^4$  of the present compounds (I). The present claimed matter may thus be considered as a novel selection of the teaching of **D1**.

**D4** and **D5** disclose amidino compounds as cathepsin inhibitors. The present compounds differ from those of **D4** and **D5** through the fragment  $-CHR^2-C(O)R^1$  on the right side of formula (I). The claimed matter is thus novel vis-à-vis **D4** and **D5**.

In view of **D3** to **D5** the application complies with the criterion of novelty.

2.2 **D1** relates to cathepsin inhibitors which generally comprise the present compounds (I). In addition, the document discloses already specific examples within the overlapping range with present claim 1 (cf. examples 1, 4, 6, 7, and 11); whereas the compounds of present claims 2 and 3 are not specifically disclosed in **D1**. In the regional phase the document is likely to become at least relevant to the question of novelty of present claim 1 and claims defined as dependent from it.

**D2** relates to  $N(R^4)(SO_2\text{phenyl and } SO_2\text{naphthyl})$  amidino compounds as cathepsin inhibitors. The present compounds differ from those of **D2** through the values of the corresponding group  $R^5$ . The document will thus not become relevant to the question of novelty of the application.

### 3 Inventive Step

3.1 The application describes the synthesis of certain compounds (I) which allegedly inhibit several cathepsins. The application, furthermore, provides protocols to evaluate the technical effect of the claimed compounds without, however, reporting any test results.

3.2 **D3** discloses already cathepsin inhibitors which generally comprise already certain present compounds (I). Although the document does not specifically disclose

compounds having exactly the present structural fragment  $-C(=NR^5)R^4$ , it shows already a structurally very similar embodiment wherein  $R^{15}$ , which corresponds with the present  $-C(=NR^5)R^4$  fragment, is pyrimidin-2-yl (cf. **D3**, page 98, lines 27-29). Furthermore, the document teaches that the left-side portion of such cathepsin inhibitors can be widely varied without loss of the desired activity (cf. claim 1,  $X^2$ ; and examples). In view of **D1** as most relevant state of the art, the problem underlying the application may be seen in the provision of further cathepsin inhibitors. Document **D4** shows further cathepsin inhibitors and teaches that the present fragments  $-C(=NR^5)R^4$  are compatible with the desired activity (cf. **D4**, claims 1, fragments A15, A16, A24, A40). It appears therefore obvious that the skilled person starting from **D1** in combination with **D4** would replace an  $R^{15}$  group of the compounds of **D1** (e.g.  $R^{15}$  pyrimidin-2-yl group of the compound of page 98) with one of the A15, A16, A24, or A40 fragments of **D4** and, thereby, arrive at the present compounds (I). The present compounds (I) are therefore considered to represent merely obvious alternatives of the compounds of **D1**. In the absence of any substantiated unexpected effect of the claimed compounds in comparison with the structurally closest related compound of **D1** (e.g. the present compound (I) wherein  $-C(=NR^5)R^4 = 1,1$ -dioxo-benzo[d]isothiazol-3-yl;  $R^3 = -CH_2SO_2CH_2Ph$ ;  $R^2 = ethyl$ ; and  $R^1 = benzoxazol-2-yl$ , compared with the compound according to page 98, lines 27-29 of **D1**), no inventive activity would be seen in the claimed subject matter. Therefore, the present claims 1-18 do at present not comply with the requirement of inventive step.

- 3.3 If the applicant, however, was able to provide convincing arguments that certain claimed compounds were not obvious in view of the cited prior art, then it is noted that the application does not provide any substantiation that the technical problem has been really solved. Under these circumstances, the only basis for accepting that the claimed compounds would solve the problem posed, would be common general knowledge. The same common general knowledge, however, would be similarly applicable to the assessment whether the solution of the technical problem is to be considered obvious. Consequently, in the absence of any substantiation of the technical effect no inventive step would be acknowledged.

#### 4 Industrial Applicability

For the assessment of the present claims 5-17 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VI**

**Certain documents cited**

**Certain published documents**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2004/000838 A1	31.12.2003	24.06.2003	24.06.2002
WO 2004/108661 A1	16.12.2004	04.06.2004	04.06.2003

**Re Item VII**

**Certain defects in the international application**

The relevant background art disclosed in D3 to D5 is not mentioned in the description, nor are these documents identified therein (Rule 5.1(a)(ii) PCT).

**Re Item VIII**

**Certain observations on the international application**

The application does not comply with the requirements of Article 6 PCT for the following reasons.

- 1 The present set of claims does not comply with the requirement of conciseness because claims 1-3 are drafted as separate independent claims, although the compounds of claims 2 and 3 appear to be comprised within the scope of claim 1.
- 2 The term "a biologic" used in claims 7, 11-15, and 18 has no clear meaning and renders the claims unclear. The definition of the objected term in the description alone is insufficient for the claims to be clear.



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- 3 Claim 5 lacks clarity because the therapeutic application is functionally defined by a mechanism of action, which does not allow any practical application in the form of a defined, real treatment of a pathological condition. The objection could be overcome by either introducing in the claim a list of pathological conditions cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition would fall within the functional definition. In addition claim 6 leaves the reader in doubt which pathological condition shall be treated by administering a compound (I). The claim is therefore not clearly defined.